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10/642,272	08/18/2003	Fumiyuki Hattori	58777.000012	3248

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EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/642,272	HATTORI ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,15-35 and 39* is/are pending in the application.

4a) Of the above claim(s) *15-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,33-35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 7, 15-35, and 39 are pending. Claims 1 and 7 are amended, claim 39 is newly added by the amendment, filed 7/28/2008.

Election/Restrictions

2. Claims 15-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/13/2006. However, Applicant's traversal arguments were not found persuasive, and the restriction requirement was made final, as set forth in the office action mailed 8/9/2006 (page 2).

Claims 1, 7, 33-35, and 39 are under consideration.

Withdrawn Objection

3. The objection to claims 1 and 7 are objected to because of a grammatical error, as set forth in the Office Action, mailed 1/28/2008 (p. 3, #4), is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7, 33-35, and 39, as amended, previously presented, and newly added, are still rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 7/28/2008 have been fully considered but they are not persuasive.

To reiterate the enablement rejection of record, the instant enablement rejection was made in part because the experiments taught by the specification do not teach a therapeutic model for chronic heart disease, ischemic heart failure, and ischemic heart disease. Therefore, the instant specification does not teach a therapeutic association between AOP-1 treatment and chronic heart disease, ischemic heart disease, or ischemic heart failure, as embraced by the claims (See page 6, last par, line 1 to page 8, line 12).

Applicant traverses this ground of rejection and asserts that Figure 2 demonstrate an association between decreased AOP-1 expression and chronic heart disease, ischemic heart failure, and ischemic heart disease (p. 8, par 2, lines 1-5). Applicant further refers to the art of Brixius et al (2007) as confirmation that this association between AOP-1 and ischemic heart failure exists in humans. Figure 2 discloses results from an experiment wherein AOP-1 transcript expression is monitored in mice with induced ischemic heart failure by ligation of the coronary artery (p. 34,

[00112] of the specification and Figure 2). Figure 2 demonstrates that AOP-1 expression decreases in the heart failure stage as compared to the hypertrophy stage of induced ischemic heart failure. The specification concludes that these results demonstrate an association between ischemic heart disease and decreased expression of AOP-1. Similarly, Brixius et al demonstrates a decrease in AOP-1 expression in human heart tissue of end stage heart failure patients as compared to normal non-failing human heart tissue (p. 826, Figure 4), demonstrating an association between AOP-1 and end stage ischemic heart failure. Examiner agrees with these conclusions from Figure 2, the specification, and Brixius et al. However, these results do not demonstrate that treatment with AOP-1 gene therapy will have a therapeutic effect on ischemic heart disease, chronic heart failure, and ischemic heart failure as claimed. Theses results only demonstrate an association between AOP-1 and progression into ischemic heart failure. No treatment was provided, specifically treatment with an AOP-1 gene as claimed. Therefore, Figure 2 and the art of Brixius et al (2007) do not provide enabling evidence that treatment with an AOP-1 gene would be therapeutic, and therefore Applicant's arguments are not found persuasive.

Applicant contests Examiner's finding that the Langendorff's method of ischemic reperfusion of the heart taught in Example 16 is a supraphysiological experimental model that is not representative of chronic heart failure, ischemic heart failure, and ischemic heart disease as discussed in the Office Action, mailed 1/28/2008 (p. 6, last par, line 1 to p. 7, line 19). Applicant states that it is widely known that ischemia is caused by a relative decrease in the number of capillaries in tissue during chronic heart

failure and refers to the art of Henquell et al (1977), Gourine et al (2004), Paternostro et al (1999). Applicant therefore concludes that the Langendorff model of cardiac ischemia is an appropriate model for ischemic heart disease (p. 8, par 3, lines 1-13 of remarks). Applicant further refers to the in vitro studies of Examples 7 and 15 as support for the Langendorf model experiments of Example 16 (p. 8, last par, line 1 to p. 9, lines 1-12).

Applicant's arguments are not found persuasive because, as previously discussed in the Office Action, mailed 1/28/2008 (p. 6, last par, line 1 to p. 7, line 19), the art of Skrzvpeic-Spring et al 2007) the Langendorff model is not a model for ischemic heart diseases. Skrzvpeic-Spring et al teaches that Langendorff model is a supraphysiological experimental model that is devoid of its natural humeral and neurological influences and therefore does not serve as an appropriate model for ischemic heart disease and therapies (p. 113, col 2, lines 117-118, and p. 120, col 2, last par). Therefore, because Skzvpeic-Spring et al teach that Langendorff model is not an appropriate model for ischemic heart disease, the results extrapolated from this method can not predictably be extrapolated to a therapeutic method of ischemic heart disease that administers an AOP-1 gene as claimed. If Applicant can provide counter evidence to suggest that the Langendorff model correlates well with therapeutic models of ischemic heart failure, ischemic heart disease, and chronic heart failure as claimed, this aspect of the enablement rejection may be overcome.

Applicant also refers to their post-filing art, Matsushima et al (2006), as evidence demonstrating the effectiveness for AOP-1 gene transfer in a chronic heart failure model

(p. 9, lines 12-16 of remarks). Matsushima et al teaches the production of a transgenic mouse that overexpresses AOP-1. Overexpression of AOP-1 in transgenic mice protected against induced myocardial infarction in said mice (p. 1784, col 1, lines 6-8). The post-filing art of Matsushima et al is not enabling for the instant invention because it encompasses a different method of introducing an AOP-1 gene into a subject. Matshushima introduces the AOP-1 into mouse embryos and expresses the AOP-1 gene constitutively because its expression is driven by a CMV promoter (p. 1780, col 1, lines 5-19). In contrast, the instant claims encompass administering AOP-1 to heart cells to produce a therapeutic effect. The administration of AOP-1 gene and the expression profiles of the AOP-1 gene are different because the method disclosed by Matshushima et al and the instantly claimed invention. Therefore, the art of Matshushima et al does not enable the instantly claimed invention because the methods are different, result in different effects, and the result from Matshushima et al can not be predictably extrapolated to the instant invention because the methods of administration and gene expression are different.

The instant enablement rejection is also being maintained because the amendments to the claims do not address all the issues of enablement previously discussed in the Office Action, mailed 1/28/2008. The amended claims still encompass a therapeutic method for any disease associated with decreased expression of an AOP-1 gene or AOP-1 by delivering a therapeutic expression vector to the heart. Therefore, the instant claims still encompass delivering a therapeutic expression vector to heart cells and treating a brain disease associated with AOP-1. This would still be considered

an indirect administration of an expression vector. As previously discussed in the Office Action, mailed 1/28/2008, the art of Tomasoni and Benigni, Guatam et al, Gunter et al, and Hajjar et al teaches that such indirect administration are highly unpredictable (p. 8, line 13 to p. 10, last line). Applicant did not provide arguments or evidence to address this issue of enablement. The specification still does not provide specific guidance for such examples of indirect administration of an AOP-1 that would predictably overcome the unpredictabilities that hinder the success of such a method. Therefore, the specification still does not enable an indirect administration of an AOP-1 gene that results in a therapeutic effect as is embraced by the instant claims.

Overall, Applicant's arguments have not been found persuasive in overcoming the issues of enablement of record. Furthermore, the claims still encompass enablement issues that were not overcome by the amendments to the claims and were not addressed by Applicant's arguments. Therefore, the enablement rejection of record is maintained.

The following rejection is necessitated by the amendments to the claims, which introduces new issues of consideration:

Written Description

5. Claims 1, 7, 33-35, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instantly amended claims are drawn to a gene therapy method that utilizes the genus of a nucleic acid having sequence identity of 90% or more to a nucleic acid encoding AOP-1 and encodes a polypeptide that retains the function of AOP-1.

In analyzing whether the written description requirement is met for genus claims, it is determined whether a representative number of species have been described by the specification. The specification discloses the an adenoviral vector comprising the nucleic acid encoding the sequence of SEQ ID NO:2, which comprises nucleic acid encoding an AOP-1 polypeptide that has the activity of treating the heart (Example 16, p. 39, [00151], lines 1 to p. 49, [00153], line 13; p. 39 Example 4, [00126], lines 3-5; and, Example 5, p. 39, [00127], line 1 to p. 40, line 6). Therefore, the specification discloses only a single species of nucleic acid encoding AOP-1 that has a therapeutic function in the heart. There are no teachings in the specification regarding which 10% of the nucleic acid can be altered to result in a nucleic acid with 90% or more identity to a nucleic acid encoding an AOP-1 polypeptide that retains the therapeutic function of AOP-1. Further, there is no disclosed or art-recognized correlation between any structure other than the AOP-1 gene of SEQ ID NO:2 and the novel function of a therapeutic effect in the heart.

An important consideration is that structure is not necessarily a reliable indicator of function. In the instant case, there is no disclosure relating similarity of the structure to conservation of function. General knowledge in the art included the knowledge that

some amino acid variations are tolerated without losing a protein's tertiary structure (Schultz et al, PRINCIPLES OF PROTEIN STRUCTURE, pp. 14-16, Spring Verlag (New York, 1979)). Therefore, given the knowledge of the art about the genetic code and its redundancies and the outcomes of substitutions on protein structure, those in the art would have likely expected the application to have been in possession of the genus of a nucleic acid comprising 90% or more identify with a nucleic acid encoding AOP-1 comprising a conserved tertiary protein structure. However, conservation of structure is not necessary a surrogate for conservation of function. In this case, there is no disclosure as to the domain(s) responsible for exacting the novel AOP-1 function of a therapeutic effect in the heart. Therefore, the absence of such crucial information would be persuasive to those of skill in art to conclude that the disclosure of a nucleic acid encoding the AOP-1 gene of SEQ ID NO:2 is not representative of other nucleic acids encoding other AOP-1 polypeptides comprising the therapeutic function in the heart.

In summary, there are no known or disclosed nucleic acids encoding AOP-1 polypeptides having the therapeutic function in the heart other than the nucleic acid sequence of SEQ ID NO:2, which comprises a AOP-1 gene. As of the filing date, there was no known or disclosed correlation between a structure other than the AOP-1 gene encoded in SEQ ID NO:2 and the therapeutic function in the heart. While general knowledge in the art may have allowed one of skill in the art to identity other nucleic acids that encode other AOP-1 polypeptides expected to have the same or similar tertiary structure, in this example there is no general knowledge in the art about the therapeutic effect in the heart of AOP-1 to suggest similarity of structure confers this

function. Accordingly one of skill in the art would not accept the disclosure by the specification of the adenoviral expression vector comprising the AOP-1 gene of SEQ ID NO:2 as representative of other nucleic acids that encode other AOP-1 polypeptides having the disclosed therapeutic function in the heart. Therefore, the specification, taken with the pre-existing knowledge in the art of amino acid substitution and the genetic code, fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the scope of the claims.

6. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632